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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,296	01/14/2000	Shu-Hsia Chen	6923-084	7224

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,296	CHEN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 38-71* is/are pending in the application.

4a) Of the above claim(s) *27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on 8/12/03 has been entered. The Examiner assigned to examine your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1632.

Claims 1-26, and 28-37 have been canceled, claims 38-71 are newly submitted and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in the 8/12/03 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENT

The prior rejection of claims 26, 28-37 applies to newly submitted claims 38-71 for reasons of record advanced in paper #15 and following.

Applicants argue that the specification teaches that fragments, derivatives and analogs of IL-12 and 4-1BBL are functionally active (wild-type IL-12 or wild type 4-1BB), that specification teaches wild-type IL-12 or wild type 4-1BB, and how to assessing the

activity of their fragments and derivatives. Thus, applicants assert that given the state of the art, the chemical structures of fragments, derivatives and analogs of IL-12 and 4-1BBL are sufficiently described.

The argument has been fully considered but they are not persuasive.

With regard to the state of the art, it is noted that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Therefore, the assertion is not properly supported. Further, even though certain fragments of IL-12 or 4-1BBL are known in the art, such as IL-12 p40, the scope of the claims are not limited to the known fragments, and not well supported by the specification.

With regard to the disclosure, simple description of wild type IL-12 or 4-1BBL is insufficient to claiming all the derivatives of the molecules because the specification fails to teach the structural-function of the wild type molecules, e.g. any consensus region that is crucial to maintain the function of the wild type molecule, and thus fails to provide sufficient description and enabling disclosure for making and using such. An adequate written description of derivative of a chemical compound requires more than a mere statement that it is part of the invention and reference to a potential method for isolating and testing it; what is required is a description of the molecule itself. It is not sufficient to define the derivatives solely by its principal biological property, i.e. **having the functionality of the wild type IL-12 or 4-1BB ligand**, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist,

in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all derivatives that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Accordingly, for reasons of record and those set forth above, the instant specification fails to meet the requirement set forth under 35 U.S.C. §112, 1st paragraph.

ENABLEMENT REQUIREMENT

The prior rejection of claims 13, 15, 17, 19, 26, and 28-37 now applies to claims 38-71, because the specification, while being enabling for increasing survival rate of a cancer patient by intratumoral injection of an adenoviral vector encoding IL-12 (Adv/mIL-12) in combination with 4-1BBL, does not reasonably provide enablement for doing so by any route of administration.

In 8/12/03 response, applicants argue, "a specification that discloses at least one method for making and using the claimed invention enables the entire scope of the claims and satisfies the enablement requirement".

The arguments have been fully considered but they are not persuasive for reasons of record and following.

The argument may apply to a pharmaceutical composition claim, but not to a method claim. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). In view of the teaching of the instant specification and the prior art of record such as those cited under §103, the anti-tumor effects are all achieved by local administration. In fact, *Colombo et al* (IDS) teach that amount of IL-12 available at the tumor site is critical for tumor regression, and *Caruso et al* teach one of the advantages for intratumoral delivery of the Adv/IL-12 is that the drug is in the vicinity of the tumor so severe systemic adverse effect is avoid (right column, page 11305). The specification fails to teach how to deliver the claimed composition from a site remote from the tumor, using any type of nucleic acid such that the composition would reach the tumor cells in sufficiently high concentration, such that a therapeutic effect could be obtained. Accordingly, the specification fails to provide an enabling disclosure to support the full scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 13, 15, 17, 19, 26, and 28-37 now applies to claims 38, 39, 42, 46, 48, 50, 52, 54, 55, 58-67, and 70 under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al*, taken with *Melero et al,* and *Vinay et al.*

In 8/12/03 response, applicants argue that Caruso does not mention 4-1BBL, and merely suggests combining Adv/mIL-12 with IL-2 and TK; Meltero does not mention IL-12, much less methods for treating cancer by administering to a subject IL-12 and 4-1BBL, and when speculates about combination therapy for treating cancer, Melero merely suggests combining B7-1 with 4-1BBL. Applicants also argue that Vinay does not teach or suggest or provide a motivation for administering IL-12 encoding nucleic acid with 4-1BBL to treat cancer.

It appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is also noted, that the test for combining references is not what the individual references themselves suggest, but rather what the

combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988).

Given that each of the cited references teaches using more than one agent for cancer therapy, it falls within the bounds of optimization as to select one agent known to have an anti-tumor effect and combine it with another. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art methods combining different cytokines and accessory molecules-all taught to be useful for the treatment of cancer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these agents to generate a new composition for the treatment of cancer with a reasonable expectation of success.

Newly submitted claims recite limitations for a fragment or derivatives of IL-12. *Caruso et al* teach inserting IL-12 p40 fragment into the E1 deleted adenoviral backbone (right column, page 11302). New claims further recite different types of cancers for treatment, since *Caruso and Melero et al* illustrated anti-tumor effects of IL-12 and 4-1BBL on three different types of tumors, and teach that IL-12 has been

effective in treating melanoma, sarcoma, and adenoma (right column, page 11305), thus it would have been obvious for the skilled artisan to use such method for treating any tumor type of interest. Therefore, the new limitations are fully taught by the combined teaching.

Accordingly, for reasons of record and those set forth foregoing, the rejection stands.

Claims 40, 41, 43-45, 47, 49, 51, 53, 54-57, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al*, *Melero et al,* and *Vinay et al* as applied to claims 38, 39, 42, 46, 48, 50, 52, 54, 55, 58-67, and 70 above, and further in view of *Goodwin et al* (US 5,674,704), and *Deetz et al* (US 5,853,714).

The claims recite limitations for using a fragment or derivatives of IL-12 and/or 4-1BBL, preferably, the human equivalent of IL-12, and 4-1BBL.

The combined teaching of *Caruso et al*, *Melero et al,* and *Vinay et al* do not specifically teach or recite a fragment or derivative of 4-1BBL. *Goodwin et al* teach using human 4-1BB ligand and certain fragments and derivatives for immune therapy (examples, and claims). *Deetz et al* provide more detailed teaching regarding human IL-12 fragments for immune therapy (column 5, lines 38-56).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Caruso et al*, *Melero et al,* and *Vinay et al* by simply substituting the murine IL-12 or 4-1BBL with humans as taught by *Goodwin et al* and *Deetz et al* with a reasonable expectation of success. The

ordinary skilled artisan would have been motivated to modify the claimed invention because it is within the knowledge of the skill to use human molecules when the subject of the treatment is human, and it is within the knowledge of the skill to select one of the art known IL-12 or 4-1BB derivatives for therapy. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
October 23, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER